GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

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What's in this week's issue?

Week of March 8 - 12, 2021

SPOTLIGHT: Alternative Treatment Modalities for Chronic Pain

- Two is Better than One in TIA/CVA
- Not so Fast: Wait-and-See Approach Non-Inferior to Early Cardioversion
- Statin Therapy Effective in Patients as Young as Six Years Old

Alternative Treatment Modalities for Chronic Pain

Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-Analysis

Garland EL, Brintz CE, Hanley AW, et al. Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-analysis [published online ahead of print, 2019 Nov 4]. *JAMA Intern Med*. 2019; 180(1):91–105.

KEY TAKEAWAY: Mind body therapies (MBT) such as medication, relaxation, and cognitive behavioral therapy (CBT) are associated with pain reduction and improvement in opioid use in adults.

STUDY DESIGN: Systematic review and meta-analysis of 60 RCT; N=6404

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: In response to the current opioid crisis, multiple studies evaluating the use of mind-body therapies as treatment for acute and chronic pain have been conducted. MBTs are emerging as possible tools for decreasing opioid use in pain management.

PATIENTS: Adults >18 years prescribed opioids for acute, chronic, procedural, and cancer pain

INTERVENTION: MBTs such as meditation, hypnosis, guided imagery, relaxation, and CBT

CONTROL: Patients being offered opioids for pain relief

OUTCOME: Primary outcome was pain severity/intensity. Secondary outcome was opioid use measured by self-report, urine toxicology, opioid misuse and disability, or functional impairment.

METHODS (BRIEF DESCRIPTION):

- A literature review of randomized controlled trials (RCT) comparing the use of MBTs with opioids for pain control and decreased use of opioids in adults age ≥ 18 years of age.
- RCTs were excluded if it did not include pain related outcomes

INTERVENTION (# IN THE GROUP): Data not provided

COMPARISON (# IN THE GROUP): Data not provided

FOLLOW UP PERIOD: 3 months

RESULTS:

Collectively MBTs (meditation, hypnosis, relaxation, suggestion studies and CBT) demonstrated significant improvement in:

- Pain reduction (29 trials, N=2916, 95% CI, -0.76 to -0.27)
- Opioid use (8 trials, N=435, 95% CI, -0.44 to -0.08)

Individually significant pain reduction was seen with:

- Meditation (3 trials, N=403, 95% CI, -1.09 to -0.31)
- Hypnosis (11 trials, N=932, 95% CI, -0.87 to -0.20)
- Suggesion Studies (3 trials, N=319, 95% CI, -1.18 to -0.18)
- CBT (4 trials, N=293, 95% CI, -0.71 to -0.15)

Significant pain reduction was NOT seen with:

- Relaxation (9 trials, N=1818, 95% CI, -1.13 to 0.22)

Meta-analysis could not be performed regarding impact of individual MBTs on opioid dosing due to variation in opioid dosing.

Pain was measured on a scale of 0–10 and opioid dose was measured in morphine equivalents.

LIMITATIONS:

- High levels of heterogeneity
- Pain duration ranged from acute to chronic
- Small sample studies
- Biases present in some trials included lack of blinding, lack of intention to treat
- Wide variation of opioids and dosing

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Two is better than one in TIA/CVA

Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

Johnston, S., Amarenco, P., Denison, H., et al, 2020. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. *New England Journal of Medicine*, 383(3), pp.207–217.

KEY TAKEAWAY: Ticagrelor plus aspirin is superior for risk reduction of composite stroke or death within 30 days but the incidence of disability was unchanged compared to aspirin alone.

STUDY DESIGN: Randomized, placebo-controlled, double-blind trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Acute ischemic strokes and transient ischemic attacks (TIAs) contribute significantly to overall morbidity and mortality. Previously, ticagrelor was not shown to be superior to aspirin in preventing vascular events or death after acute ischemic strokes or TIAs. The benefit of combined ticagrelor and aspirin has not been well studied.

PATIENTS: Patients > 40 years of age with either mild–moderate acute noncardioembolic ischemic stroke or high-risk TIA or symptomatic intra/extracranial arterial stenosis (>50%) that could account for TIA symptoms

INTERVENTION: 180mg 1 time PO dose of ticagrelor followed by 90mg PO every 12 hours for 30 days in addition to aspirin PO daily (75-100mg)

CONTROL: Aspirin PO daily (75-100mg) and placebo pill every 12 hours

OUTCOME: Composite of stroke or death from randomization through 30 days of follow up
Secondary: The first subsequent ischemic stroke and incidence of disability within 30 days

METHODS (BRIEF DESCRIPTION):

- Participants were screened with the inclusion criteria and confirmed absence of an intracranial hemorrhage or other explanation for the current symptoms.
- Patients randomized 1:1 to intervention or control group within 24 hours of symptom onset.
- Patients were monitored at 5-9 days, 30-34 days, and 60-64 days.
- The participants were monitored for composite stroke or death.
- The incidence of overall disability was measured with the modified Rankin scale.
- Analysis was by intention to treat.

INTERVENTION (# IN THE GROUP): 5523
COMPARISON (# IN THE GROUP): 5493

FOLLOW UP PERIOD: Patients were followed for 60 days total. First, 30-days of trial treatment were followed by an additional 30 days, with continued collection of data on outcome and safety events.

RESULTS:

- Stroke or death occurred in 5.5% of the intervention group vs 6.6% of the control group. (HR 0.83; 95% CI 0.71–0.96; P=0.02, NNT 91)
- Acute ischemic stroke occurred in 5.0% of the intervention group vs 6.3% in the control group. (HR 0.79; 95% CI 0.68–0.93; P=0.004, NNT 77)
- No statistically significant difference in disability level between the intervention and control group.
- Severe bleeding occurred more frequently in the intervention group (0.5%) vs the control group (0.1%). (HR 3.99; 95% CI, 1.74–9.14; P=0.001, NNH 250)

LIMITATIONS:

- Industry/AstraZeneca funded study
- In both the experimental and control arm of the study 14.3% and 11.7% discontinued trial treatment prematurely.
- Not equally distributed across different races (~53% white, ~42% Asian, and ~0.5% black).

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Not so Fast: Wait-and-see approach non-inferior to early cardioversion in recent-onset Atrial Fibrillation

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation: Randomized, Open-Label, Noninferiority Trial

Pluymaekers NA, Dudink EA, Luermans JG, et al. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. *New England Journal of Medicine*. 2019; 380(16):1499–1508.

KEY TAKEAWAY: For recent-onset, hemodynamically stable, symptomatic atrial fibrillation, delayed cardioversion (rate control) is no worse than immediate cardioversion in achieving sinus rhythm at 4 weeks.
STUDY DESIGN: A multicenter, randomized, open-label, non-inferiority trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients commonly undergo immediate pharmacologic or electrical cardioversion to restore sinus rhythm which may be unnecessary as spontaneous conversion to sinus rhythm occurs frequently. Early cardioversion may lead to unnecessary hospitalization and over treatment which may lead to poor use of resources, time, and money.
PATIENTS: 18 years of age or older (mean age 65) with recent-onset (< 36 hr), hemodynamically stable, symptomatic atrial fibrillation without signs of myocardial ischemia or a history of persistent atrial fibrillation
INTERVENTION: Delayed cardioversion in a wait-and-see method using rate-control medications
CONTROL: Early cardioversion
OUTCOME: Presence of sinus rhythm on EKG in the outpatient clinic at 4 weeks
METHODS (BRIEF DESCRIPTION): Patients with hemodynamically stable, symptomatic atrial fibrillation who presented to the emergency department were randomized to rate control therapy with medications vs pharmacologic/electrical early cardioversion. Rate-control medications included IV or oral β-blockers, nondihydropyridine calcium channel blockers, or digoxin. These medications were given at various doses to help control symptoms and heart rate to 110 bpm or less. Early cardioversion consisted of pharmacologic cardioversion, using flecainide. Electrical cardioversion was used in patients with contraindications to pharmacologic cardioversion and with previous or current unsuccessful pharmacologic cardioversion. Both groups received anticoagulation per current standards. Patients were followed up in 4 weeks' time at an outpatient clinic to assess for sinus rhythm via EKG.

INTERVENTION (# IN THE GROUP): 218
COMPARISON (# IN THE GROUP): 219

FOLLOW UP PERIOD: 4 weeks

RESULTS: The primary outcome showed no statically significant difference in delayed vs early cardioversion. The 95% Confidence interval –8.2 to 2.2 (P = 0.005) met criteria for non-inferiority suggesting rate control therapy was no worse than early cardioversion. The two groups had a similar incidence of recurrence of atrial fibrillation (HR 0.97; 95% CI, 0.65–1.43).

LIMITATIONS: The study was not powered sufficiently to evaluate for safety.

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Statin Therapy Effective in Patients as Young as Six Years Old

Intermediate-Term Efficacy and Tolerance of Statins in Children

Mamann N, Lemale J, Karsenty A, et al. Intermediate-Term Efficacy and Tolerance of Statins in Children. *J Pediatr*. 2019; 210:161–165.

KEY TAKEAWAY: Statin therapy is efficacious, safe, and well-tolerated in children and adolescents for intermediate-term management of familial hypercholesterolemia.

STUDY DESIGN: Prospective cohort study of single non-randomized cohort as compared to standardized normal values.

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: United States Preventive Services Taskforce (USPTF) provides recommendations for primary preventative statin therapy for adults but not children. This study provides evidence for statin therapy in children.

PATIENTS: Children with familial hypercholesterolemia and a first degree relative with a cardiovascular event before 55 years old if male or 60 years old if female

INTERVENTION: Treatment with pravastatin, rosuvastatin, or atorvastatin for average 14.3 years

CONTROL: Age-matched general population

OUTCOME: Lipid profile; clinical & biological treatment tolerability

METHODS (BRIEF DESCRIPTION):

- Participants were selected from those receiving care at Trousseau Hospital in Paris France
- Inclusion Criteria: Participants were identified as having familial hypercholesterolemia by:
  - Analysis of heterozygous genetic mutations (LDLR, apolipoprotein B-100, proprotein convertase subtilisin/kexin type 9 gene) OR LDL–C >190mg/dL despite 6 months on a lipid-lowering diet
  - AND a first degree relative with hypercholesterolemia or cardiovascular events (angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary artery bypass, ischemic stroke, sudden cardiac death or peripheral artery disease)
- Exclusion Criteria: Participants with homozygous genetic FH mutations
- All participants were advised to follow a lipid-lowering diet starting 6 months before initiation of statin therapy
- Participants were excluded if the dietary modifications resulted in improved LDL-C to below 160mg/dL with risk factors (obesity, diabetes, hypertension or lipoprotein (a) >500mg/L, high blood pressure) or to below 190mg/dL with no risk factors
- Participants were started on pravastatin (n=101, median age 9.9 y/o), rosuvastatin (n=22, median age 9.9 y/o) or atorvastatin (n=8, median age 12.0 y/o), starting at the smallest dose and increased to the maximal allowable dose (pravastatin 20 mg for 0–13 y/o and 40 mg for 13–18 y/o; rosuvastatin 10 mg for 0-9 y/o and 20 mg for 9–18 y/o; atorvastatin 40 mg for 0–18 y/o).
- Participants' lipid profile, liver and muscle enzymes, growth and pubertal development, and self-reported side effects were monitored

INTERVENTION (# IN THE GROUP): 131

COMPARISON (# IN THE GROUP): Normal values in general population for respective age

FOLLOW UP PERIOD: 2.3 months to 22.5 years (median 14.3 years; average 10.4 visits)

RESULTS:

Statin therapy is effective in improving the lipid profile in children with the following median changes from baseline:

- A decrease of 24.4% in total cholesterol (p<.0001)
- A decrease of 32% in LDL-C (p<.0001)
- A decrease of 1.6% in triglycerides (p<.025)
- An increase of 6% in HDL (p<.8)

Statin therapy is safe and well-tolerated in children and adolescents:

- 81% reported no side effects
- 12% experienced muscular symptoms
- 3.8% had elevated CPK
- No patients with elevations in AST and ALT following treatment

LIMITATIONS:

- Relatively small, single-center study (Parisian population)
- Side effects self-reported by children and may be unrelated to statin use
- No placebo-controlled group
- While this is a longer study (2.3mo to 22.5yr) than previously published, it cannot be used to predict the efficacy, safety, and tolerance of long-term statin therapy initiated in childhood or adolescence, nor does it assess the rates or changes in rates of cardiovascular morbidity or mortality in adulthood.

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